Comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes: A multicenter, randomized, active-controlled, open-label, parallel design clinical trial

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Abstract

Background: Alpha-glucosidase inhibitors or dipeptidyl peptidase-4 inhibitors are both hypoglycemia agents that specifically impact on postprandial hyperglycemia. We compared the effects of acarbose and sitagliptin add on to metformin on time in range (TIR) and glycemic variability (GV) in Chinese patients with type 2 diabetes mellitus through continuous glucose monitoring (CGM).

Methods: This study was a randomized, open-label, active-controlled, parallel-group trial conducted at 15 centers in China from January 2020 to August 2022. We recruited patients with type 2 diabetes aged 18–65 years with body mass index (BMI) within 19–40 kg/m^2 and hemoglobin A1c (HbA1c) between 6.5% and 9.0%. Eligible patients were randomized to receive either metformin combined with acarbose 100 mg three times daily or metformin combined with sitagliptin 100 mg once daily for 28 days. After the first 14-day treatment period, patients wore CGM and entered another 14-day treatment period. The primary outcome was the level of TIR after treatment between groups. We also performed time series decomposition, dimensionality reduction, and clustering using the CGM data.

Results: A total of 701 participants received either acarbose or sitagliptin treatment in combination with metformin. There was no statistically significant difference in TIR between the two groups. Time below range (TBR) and coefficient of variation (CV) levels in acarbose users were significantly lower than those in sitagliptin users. Median (25th percentile, 75th percentile) of TBR below target level <3.9 mmol/L ($TBR_{3.9}$): Acarbose: 0.45% (0, 2.13%) *vs*. Sitagliptin: 0.78% (0, 3.12%), $P = 0.042$; Median (25th percentile, 75th percentile) of TBR below target level <3.0 mmol/L ($TBR_{3.0}$): Acarbose: 0 (0, 0.22%) *vs*. Sitagliptin: 0 (0, 0.63%), $P = 0.033$; CV: Acarbose: 22.44 ± 5.08% *vs*. Sitagliptin: 23.96 ± 5.19%, $P < 0.001$. By using time series analysis and clustering, we distinguished three groups of patients with representative metabolism characteristics, especially in GV (group with small wave, moderate wave and big wave). No significant difference was found in the complexity of glucose time series index (CGI) between acarbose users and sitagliptin users. By using time series analysis and clustering, we distinguished three groups of patients with representative metabolism characteristics, especially in GV.

Conclusions: Acarbose had slight advantages over sitagliptin in improving GV and reducing the risk of hypoglycemia. Time series analysis of CGM data may predict GV and the risk of hypoglycemia.

Trial Registration: Chinese Clinical Trial Registry: ChiCTR2000039424.

Keywords: Glycemic variability; Continuous glucose monitoring; Acarbose; Sitagliptin; Time series analysis; Diabetes

Introduction

Continuous glucose monitoring (CGM) is widely used in patients with diabetes over the past few years. CGM has its advantages on assessing glucose control and glycemic variability (GV), especially on identifying hypoglycemia and hyperglycemia, which is of considerable value in clinical decision-making.[1]

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Postprandial glucose excursion is a major contributor to glucose excursion. Alpha-glucosidase inhibitors (AGIs) or dipeptidyl peptidase-4 inhibitors (DPP-4is) are both hypoglycemia agents that specifically impact on postprandial hyperglycemia. Various studies have shown that AGIs[2–5] and DPP-4is[6,7] play an important role in reducing GV. However, seldom well-designed randomized controlled trials was found comparing the effects of these two drugs on glucose control and GV.

CGM data characterize glucose dynamics instead of showing diabetic statuses at a special time-point, thus they possess the characteristics of time series. Quantifying the complexity of glucose time series with refined composite multi-scale entropy (RCMSE) algorithm[8] has gained considerable attention in recent years. Using RCMSE analysis, Li *et al*[9] found that there is a progressive loss of complexity in the glucose dynamics from health to prediabetes and then to diabetes, suggesting that complexity analysis of glucose dynamics may be an effective tool for tracking the progression of diabetes. Moreover, there are few studies expanding the application of CGM in patients with type 2 diabetes through time series analysis.[10,11]

Therefore, the objective of this study was to compare the effects of acarbose and sitagliptin add on to metformin on glucose control, GV and the complexity of glucose time series in Chinese patients with type 2 diabetes. We also performed time series decomposition, dimensionality reduction, and clustering using CGM data to explore precision medicine approach based on time series analysis.

Methods

Study design and participants

This study was a randomized, open-label, active-controlled, parallel-group trial conducted at 15 centers in China from January 2020 to August 2022 [Supplementary Notes, http://links.lww.com/CM9/C303]. The study protocol was prepared according to the revised *Helsinki Declaration* for Biomedical Research Involving Human Subjects and Guidelines for Good Clinical Practice. The study was approved by ethics committees of all participating centers before implementation, and all included patients provided their written informed consent. The study was registered at https://www.chictr.org.cn (ChiCTR2000039424).

This study enrolled patients with type 2 diabetes aged 18–65 years, with body mass index (BMI) of 19–40 kg/m^2, and hemoglobin A1c (HbA1c) level between 6.5% and 9.0%, who had been previously treated with metformin combined with either AGIs or DPP-4is for at least 1 month. Key exclusion criteria and the trial protocol are available in Supplementary Materials, http://links.lww.com/CM9/C303.

Randomization

Given the open-label nature of the intervention, treatment assignment was generated using a simple randomization scheme (i.e., no stratification).

Interventions

All eligible patients were randomly assigned in a 1:1 ratio to receive either acarbose chewable tablet (50 mg/tablet, Hangzhou Zhongmei Huadong Pharmaceutical Co. Ltd., Hangzhou, China) 100 mg three times daily combined with metformin (500 mg/tablet, Shanghai Zhongmei Bristol-Myers Squibb Pharmaceutical Co. Ltd., Shanghai, China, maintain the previous dose) or sitagliptin (100 mg/tablet, Hangzhou Merck Pharmaceutical Co. Ltd.) 100 mg once daily combined with metformin for 28 days. To ensure stability and reliability of the CGM data, we extended the wearing time to 14 days. After the initial 14-day treatment period, patients would wear CGM (FreeStyle Libre [FSL]; Abbott Diabetes Care, Witney, UK) for another 14-day treatment period.

We used the hospital version of FSL, which were blinded to the participants. Interstitial fluid glucose levels were measured every 15 min for 14 days at the back of the upper arm of patients. The CGM data were stored in the receiving part device and downloaded to a computer. The original CGM data included glucose measurement values (in mmol/L) and measuring time (in minutes).

The visual image of the clinical trial is shown as Figure 1.

Outcomes

The primary endpoint was time in range (TIR, 3.9–10.0 mmol/L). The secondary endpoints included time below range (TBR, below target level <3.9 mmol/L or 3.0 mmol/L), time above range (TAR, above target level >10.0 mmoL/L or 13.9 mmoL/L), glycemia risk index (GRI), coefficient of variation (CV), standard deviation (SD), and mean amplitude of glycemic excursions (MAGE), the complexity of glucose time series index (CGI), and the entropy at time scales of 1–6 (corresponding to the period of 15 to 90 min, details were shown in Supplementary material, http://links.lww.com/CM9/C303).

Variables calculation

TIR was calculated as the number of mean glucose values at 3.9–10.0 mmol/L divided by the number of total values multiplied by 100. TBR (below target level <3.9 mmol/L or 3.0 mmol/L, expressed as $TBR_{3.9}$ or $TBR_{3.0}$) and TAR (above target level >10.0 mmoL/L or 13.9 mmoL/L, expressed as $TAR_{10.0}$ or $TAR_{13.9}$) were calculated in a similar way. Postprandial TIRs (TBR, TAR) refer to specific values at 7:00–10:00, 12:00–15:00, and 18:00–21:00, respectively. Daytime refers to 7:00–21:59, while nocturnal refers to 21:00–6:59.

GRI will be calculated as (3.0 × VLow) + (2.4 × Low) + (1.6 × VHigh) + (0.8 × High), where VLow represents the percentage of time in very low-glucose hypoglycemia (<3.0 mmol/L), Low represents the percentage of time in low-glucose hypoglycemia (≥3.0 to <3.9 mmol/L), High represents the percentage of time in high-glucose hyperglycemia (>10.0 to ≤13.9 mmol/L), and VHigh represents very high-glucose hyperglycemia (>13.9 mmol/L).[12]

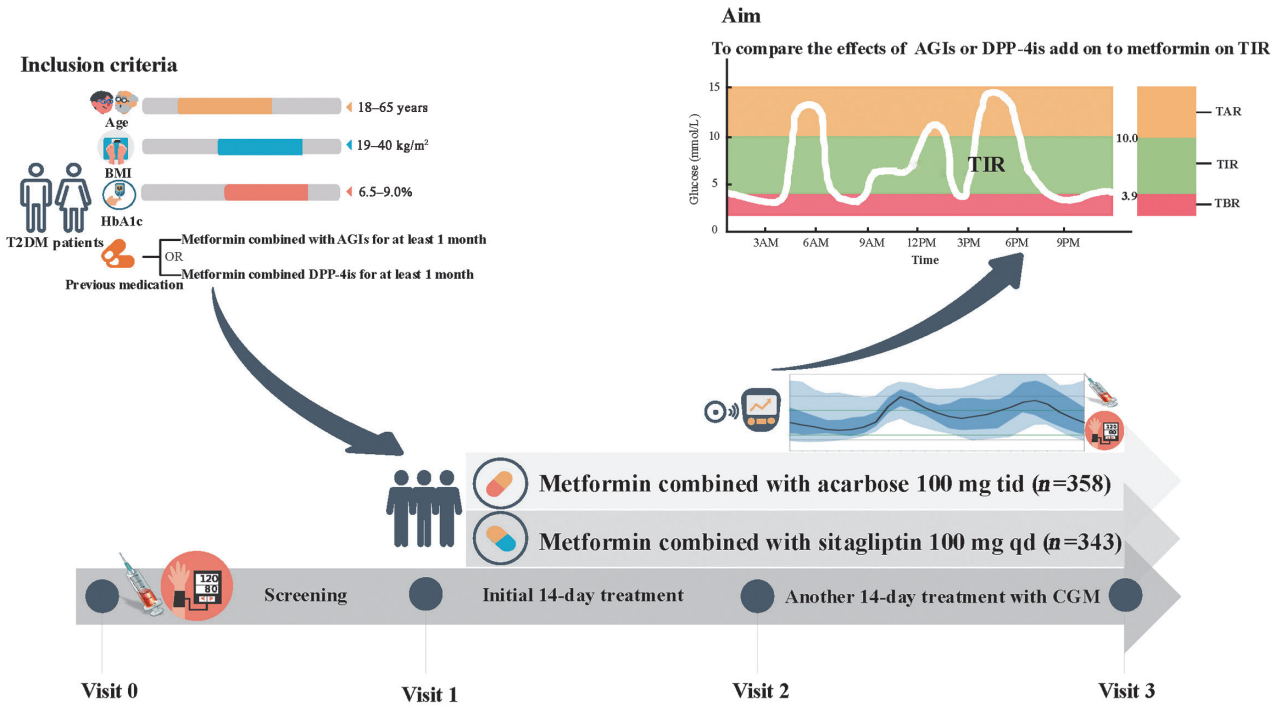

Figure 1: Visual image of the clinical trial of comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes. AGIs: Alpha-glucosidase inhibitors; CGM: Continuous glucose monitoring; DPP-4is: Dipeptidyl peptidase-4 inhibitors; HbA1c: Hemoglobin A1c; Qd: Once daily; TIR: Time in range; Tid: Three times a day.

Daily CV was calculated as daily SD divided by the mean glucose value multiplied by 100. CV was calculated as the average of daily CV. MAGE was calculated as the average of all blood glucose (BG) increases or decreases that are >1 SD of all BG measures.[13]

We also performed time series decomposition, dimensionality reduction, and clustering using CGM data. The detailed process of RCMSE algorithm and time series analysis is shown in Supplementary Materials, http://links.lww.com/CM9/C303.

Sample size calculation

If TIR was 60% at baseline in both acarbose and sitagliptin groups, to reach a 10% difference between groups at the end of the trial, we would need 594 patients to prove that TIR in acarbose group is non-inferior to that in sitagliptin group, with an 80% possibility at a two-sided *P*-value of 0.05. Considering the possibility of a 20% missing rate, the minimum sample size was 744 for randomization.

Statistical analyses

Continuous variables were reported as mean (SD) for normally distributed data, median (25th percentile, 75th percentile) for non-normally distributed data, and were compared using *t* test or Mann–Whitney *U* test. Categorical variables were presented as number (%) and were compared using chi-squared tests or Fisher's test.

Three groups were identified after time series decomposition, dimensionality reduction and clustering: group with small wave (Group 1), group with moderate wave (Group 2) and group with big wave (Group 3). Continuous variables were compared using analysis of variance and Kruskal–Wallis test. Categorical variables were compared using the chi-squared test. Spearman's rank correlation was used for correlation analysis.

P <0.05 was considered as statistically significant. The statistical analysis was performed using IBM SPSS Statistics 27.0 software (SPSS, Armonk, NY, USA) and Google Colab (Python 3.8, https://colab.research.google.com).

Results

Patient characteristics

A total of 744 patients were screened, of whom 710 were randomized (sitagliptin 100 mg once a day: 350 patients; acarbose 100 mg three times a day: 360 patients) [Figures 1 and 2]. Among them, 358 patients were treated with acarbose add on metformin, and 343 patients were treated with sitagliptin add on metformin. Ultimately, 329 participants in the acarbose group and 322 participants in the sitagliptin group completed study. While the analysis retained the initial sample sizes of 358 patients and 343 patients per group. Baseline demographics and clinical characteristics were comparable across the treatment groups [Table 1]. The mean ± SD of age, BMI, and HbA1c were 53.11 ± 9.40 years, 25.73 ± 3.38 kg/m^2, and 7.30 ± 1.03%, respectively. A total of 386/596 (64.77%) patients had type 2 diabetes for ≤60 months and 210/596 (35.23%) for over 60 months (596 participants retained analyzable disease course data).

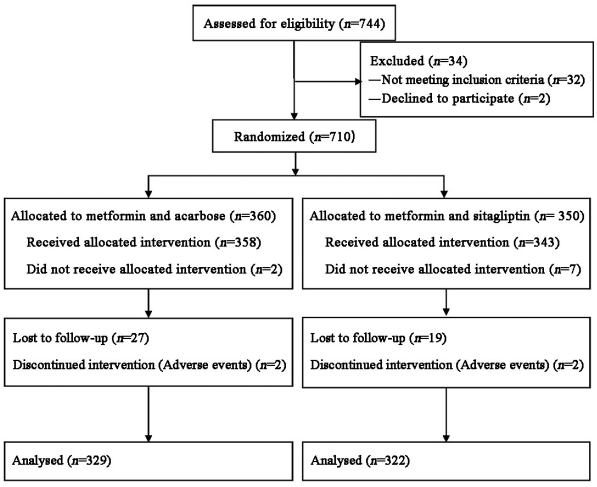

Figure 2: Flowchart of patient's enrollment included in the trial of comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes.

Glucose control

TIR was 89.15% (78.12%, 95.07%) in acarbose treatment and 88.72% (77.44%, 94.73%) in sitagliptin treatment, with no significant difference between the groups ($P = 0.305$) [Table 1 and Supplementary Figure 1, http://links.lww.com/CM9/C303].

Compared with sitagliptin, $TBR_{3.9}$ in acarbose treatment was significantly lower (Acarbose: 0.45% [0, 2.13%] *vs*. Sitagliptin: 0.78% [0, 3.12%], $P = 0.042$), so was $TBR_{3.0}$ (Acarbose: 0 [0, 0.22%] *vs*. Sitagliptin: 0 [0, 0.63%], $P = 0.033$). While $TAR_{10.0}$ (Acarbose: 7.29% [2.32%, 17.10%] *vs*. Sitagliptin: 7.59% [2.39%, 17.65%], $P = 0.792$) was comparable between groups. When concerning hypoglycemia lasting ≥15 min, acarbose-treated patients had more episodes of continuous hypoglycemia ($TBR_{3.0}$: Acarbose: 0 [0, 3.00] *vs*. Sitagliptin: 0 [0, 4.00], $P = 0.043$).

GRI was also comparable between groups (Acarbose: 11.78 [5.32, 26.05] *vs*. Sitagliptin: 13.90 [7.44, 26.13], $P = 0.137$).

Post-breakfast TIR was significantly higher in acarbose-treated patients than those in sitagliptin-treated patients (Acarbose: 89.29% [75.60%, 97.22%] *vs*. Sitagliptin: 86.11% [68.92%, 95.34%], $P = 0.009$), and post-breakfast $TAR_{10.0}$ was significantly lower in acarbose-treated patients (Acarbose: 7.69% [1.79%, 21.43%] *vs*. Sitagliptin: 10.71% [2.98%, 26.79%], $P = 0.039$). In the early stage (first 5 days) and middle stage (middle 5 days) of CGM wearing, and either by night or by day, TBR in acarbose-treated patients was significantly lower than that in sitagliptin-treated patients (all $P < 0.05$) [Table 1].

GV

Compared with sitagliptin, CV was significantly lower in acarbose treatment (Acarbose: 21.88% [18.81%, 25.10%] *vs*. Sitagliptin: 23.71% [20.07%, 27.12%], $P < 0.001$). Although SD (Acarbose: 1.57 [1.32, 1.91] mmol/L *vs*. Sitagliptin: 1.68 [1.34, 2.01] mmol/L, $P = 0.052$) and MAGE (Acarbose: 4.36 [3.42, 5.25] mmol/L *vs*. Sitagliptin: 4.49 [3.67, 5.51] mmol/L, $P = 0.103$) in acarbose-treated patients were lower than those in sitagliptin-treated patients, no significant differences were found between the two groups [Table 1].

Complexity of glucose time series

RCMSE analysis showed that there were no significant differences in CGI and the sample entropies at time scales of 1–6 between acarbose-treated and sitagliptin-treated patients (all $P > 0.05$) [Supplementary Table 1 and Supplementary Figure 2, http://links.lww.com/CM9/C303].

Spearman correlation suggested that CGI was positively correlated with baseline body weight, BMI, fasting plasma glucose (FPG), fasting C-peptide, and TIR, and negatively correlated with CV, SD, MAGE, TAR, and GRI in patients with type 2 diabetes (all $P < 0.05$) [Supplementary Table 2 and Supplementary Figure 3, http://links.lww.com/CM9/C303].

Changes of FPG, GA, HbA1c, fasting insulin, fasting C-peptide, HOMA-IR and Homeostasis Model Assessment of beta-cell Function (HOMA-β), the mean BG levels, and the response rates are shown in Supplementary Table 3, http://links.lww.com/CM9/C303. HOMA-β in sitagliptin-treated patients increased more significantly than that in acarbose-treated patients (Sitagliptin *vs*. Acarbose: 5.28 [–7.10, 20.17] *vs*. 0.42 [–12.84, 16.37], $P = 0.017$).

Safety and tolerability

Number of patients with safety endpoints data was 301 and 291 in Acarbose or sitagliptin treatment group respectively. Adverse events were reported in 4/301 (1.33%) and 4/291 (1.37%) of participants in the acarbose and sitagliptin groups respectively. There were one nausea, two diarrhea, and one gastrointestinal hemorrhage reported in the acarbose group. One nausea, one diarrhea, one acute myocardial infarction, and one rash were reported in the sitagliptin group. No severe hypoglycemia cases requiring assistance were reported. No significant difference in the incidence of adverse events was found between groups. No significant differences in the changes of blood pressure, liver and renal function, and peripheral blood cells were found between groups [Table 2]. The scores of diabetes treatment satisfaction questionnaire (DTSQs) in the two groups are shown in Supplementary Table 4, http://links.lww.com/CM9/C303.

Time series analysis

We subjectively designated three groups according to the graphic features of the diagram: group with small wave (Group 1), group with moderate wave (Group 2) and group with big wave (Group 3). Consequently, Group 1 (208 patients) consisted of Cluster 1 and 2 of the original clusters, Group 2 (101 patients) consisted of Cluster 3, and Group 3 (195 patients) consisted of

Table 1: Major characteristics of study participants included in the trial of comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes.

Items	Acarbose (*N* = 358)	Sitagliptin (*N* = 343)	Statistical values	*P*-value
Male	208 (58.10)	189 (55.10)	0.641	0.423
Age (years)	55.00 (47.00, 60.00)	55.00 (47.00, 60.00)	0.307	0.759
Duration of diabetes (months)	48.00 (24.00, 84.00)	48.00 (24.00, 84.00)	–0.694	0.488
Body weight (kg)	72.00 (65.00, 80.00)	70.00 (63.00, 79.00)	–2.536	0.011
BMI (kg/m^2)	25.60 (23.70, 28.10)	25.30 (23.20, 27.20)	–1.817	0.069
SBP (mmHg)	125.00 (120.00, 135.00)	125.00 (120.00, 133.00)	0.070	0.944
DBP (mmHg)	78.00 (70.00, 83.00)	78.00 (70.00, 83.00)	0.094	0.925
ALT (U/L)	20.59 (15.00, 31.10)	23.00 (17.00, 31.00)	1.815	0.070
AST (U/L)	19.00 (16.00, 23.00)	20.00 (17.00, 24.00)	3.528	0.001
Scr (μmol/L)	68.10 (58.28, 78.40)	67.90(58.00, 76.60)	0.556*	0.578
eGFR (ml·min^{-1}·1.73m^{-2})	98.60 (90.22, 109.08)	98.93 (86.21, 109.80)	–0.461	0.645
FPG (mmol/L)	7.47 (6.53, 8.47)	7.38 (6.50, 8.44)	–0.598	0.550
GA (%)	16.32 (14.40, 18.96)	16.29 (14.38, 18.41)	–0.525	0.600
HbA1c (%)	7.10 (6.68, 7.70)	7.10 (6.62, 7.80)	0.066	0.948
Fasting insulin (μU/mL)	9.82 (6.63, 15.34)	9.47 (6.10, 13.81)	–0.828	0.408
Fasting C-peptide (ng/mL)	1.70 (1.15, 2.49)	1.67 (1.12, 2.43)	–0.221	0.825
HOMA-β	48.55 (30.20, 84.62)	46.76 (30.26, 78.20)	–0.754	0.451
HOMA-IR	3.21 (2.08, 5.28)	3.13 (1.98, 4.86)	–0.858	0.391
CV (%)	21.88 (18.81, 25.10)	23.71 (20.07, 27.12)	3.785	0.001
SD (mmol/L)	1.57 (1.32, 1.91)	1.68 (1.34, 2.01)	1.939	0.052
MAGE (mmol/L)	4.36 (3.42, 5.25)	4.49 (3.67, 5.51)	1.630	0.103
TIR (%)	89.15 (78.12, 95.07)	88.72 (77.44, 94.73)	–1.025	0.305
$TAR_{10.0}$ (%)	7.29 (2.32, 17.10)	7.59 (2.39, 17.65)	0.264	0.792
$TAR_{13.9}$ (%)	0.15 (0, 1.49)	0.15 (0, 1.45)	–0.070	0.944
$TBR_{3.9}$ (%)	0.45 (0, 2.13)	0.78 (0, 3.12)	2.036	0.042
$TBR_{3.0}$ (%)	0 (0, 0.22)	0 (0, 0.63)	2.137	0.033
$TBR_{3.9}$ ≥15 min (No.)	1.00 (0, 5.00)	2.00 (0, 6.00)	–1.556	0.120
$TBR_{3.0}$ ≥15 min (No.)	0 (0, 3.00)	0 (0, 4.00)	–2.027	0.043
GRI	11.78 (5.32, 26.05)	13.90 (7.44, 26.13)	1.489	0.137
Post-breakfast				
TIR (%)	89.29 (75.60, 97.22)	86.11 (68.82, 95.34)	–2.626	0.009
$TAR_{10.0}$ (%)	7.69 (1.79, 21.43)	10.71 (2.98, 26.79)	2.061	0.039
$TAR_{13.9}$ (%)	0 (0, 1.19)	0 (0, 1.79)	0.944	0.345
$TBR_{3.9}$ (%)	0	0 (0, 0.60)	1.572	0.116
$TBR_{3.0}$ (%)	0	0	0.686	0.492
Post–lunch				
TIR (%)	86.54 (71.44, 95.24)	84.87 (67.26, 94.49)	–1.492	0.136
$TAR_{10.0}$ (%)	10.26 (1.79, 26.28)	10.81 (2.38, 30.75)	0.840	0.401
$TAR_{13.9}$ (%)	0 (0, 1.79)	0 (0, 2.04)	–0.108	0.914
$TBR_{3.9}$ (%)	0 (0, 1.19)	0 (0, 1.79)	1.400	0.161
$TBR_{3.0}$ (%)	0	0	1.086	0.277
Post–dinner				
TIR (%)	88.62 (72.02, 95.83)	80.10 (72.02, 96.07)	0.095	0.924
$TAR_{10.0}$ (%)	9.52 (1.79, 27.53)	8.00 (1.19, 26.12)	–0.691	0.490
$TAR_{13.9}$ (%)	0 (0, 1.82)	0 (0, 1.19)	–0.705	0.481
$TBR_{3.9}$ (%)	0 (0, 0.60)	0 (0, 1.19)	0.748	0.455
$TBR_{3.0}$ (%)	0	0	1.091	0.275
Daytime				
TIR (%)	86.99 (73.93, 94.49)	85.90 (71.23, 94.11)	–1.047	0.295
$TAR_{10.0}$ (%)	10.56 (3.29, 22.93)	11.05 (3.33, 24.00)	0.381	0.703
$TAR_{13.9}$ (%)	0.22 (0, 2.14)	0.14 (0, 2.67)	0.099	0.921
$TBR_{3.9}$ (%)	0.11 (0, 1.47)	0.37 (0, 2.24)	2.487	0.013
$TBR_{3.0}$ (%)	0	0 (0, 0.13)	1.853	0.064
Nocturnal				
TIR (%)	94.68 (84.46, 98.70)	92.78 (85.69, 97.82)	–1.706	0.088
$TAR_{10.0}$ (%)	1.11 (0, 5.96)	0.93 (0, 7.06)	–0.117	0.907
$TAR_{13.9}$ (%)	0	0	–0.598	0.550

(*continued*)

Table 1

(Continued)

Items	Acarbose ($N = 358$)	Sitagliptin ($N = 343$)	Statistical values	*P*-value
$TBR_{3.9}$ (%)	0.56 (0, 3.89)	1.01 (0, 6.80)	1.823	0.068
$TBR_{3.0}$ (%)	0 (0, 0.24)	0 (0, 1.14)	2.304	0.021
First 5 days				
TIR (%)	88.58 (77.55, 95.15)	86.55 (74.91, 93.83)	–1.531	0.126
$TAR_{10.0}$ (%)	6.74 (1.83, 18.24)	7.24 (1.95, 20.67)	0.571	0.568
$TAR_{13.9}$ (%)	0 (0, 1.37)	0 (0, 1.67)	0.898	0.369
$TBR_{3.9}$ (%)	0.48(0, 3.41)	0.94 (0, 4.95)	1.944	0.052
$TBR_{3.0}$ (%)	0 (0, 0.24)	0 (0, 0.86)	1.970	0.049
Middle 5 days				
TIR (%)	90.83 (78.96, 97.66)	90.21 (77.29, 96.67)	–1.348	0.178
$TAR_{10.0}$ (%)	7.09 (1.67, 18.86)	7.92 (2.08, 19.58)	0.991	0.322
$TAR_{13.9}$ (%)	0 (0, 1.46)	0 (0, 1.04)	–0.674	0.500
$TBR_{3.9}$ (%)	0 (0, 0.21)	0 (0, 0.63)	2.325	0.020
$TBR_{3.0}$ (%)	0	0	0.985	0.325
Last 5 days				
TIR (%)	90.82 (78.66, 96.53)	90.23 (77.49, 96.68)	–0.160	0.873
$TAR_{10.0}$ (%)	5.87 (1.40, 17.06)	5.34 (1.42, 15.40)	–0.472	0.637
$TAR_{13.9}$ (%)	0 (0, 1.19)	0 (0, 0.91)	–0.111	0.912
$TBR_{3.9}$ (%)	0 (0, 0.94)	0 (0, 1.74)	1.766	0.077
$TBR_{3.0}$ (%)	0	0	0.793	0.428

Continuous variables were reported as median (25th percentile, 75th percentile). Categorical variables were presented as number (%). Comparisons between groups were performed using *t* test* or Mann–Whitney *U* test. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CV: Coefficient of variation; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; GA: Glycosylated albumin; GRI: Glycemia risk index; HbA1c: Hemoglobin A1c; HOMA: Homeostasis model assessment of beta cell function; HOMA-IR: Homeostasis model assessment of insulin resistance; HR: Heart rate; MAGE: Mean amplitude of glycemic excursions; SBP: Systemic blood pressure; Scr: Serum creatinine; SD: Standard deviation; TAR: Time above range; TBR: Time below range; TIR: Time in range.

Table 2: Safety endpoints of study participants included in the trial of comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes.

Variables	Acarbose ($N = 301$)	Sitagliptin ($N = 291$)	Statistical values	*P*-value
Adverse events No. (%)	4 (1.33)	4 (1.37)	–	0.619
Hypoglycemia events No. (%)	0	0	–	–
Body weight changes (kg)	0 (–0.50, 0)	0 (–0.70, 0)	0.150	0.880
BMI changes (kg/m2)	0 (–0.30, 0)	0 (–0.20, 0)	1.090	0.276
SBP changes (mmHg)	0 (–7.00, 6.00)	0 (–6.25, 5.00)	–0.784	0.433
DBP changes (mmHg)	0 (–5.00, 5.00)	0 (–6.00, 4.00)	–0.324	0.746
ALT changes (U/L)	0.30 (–6.00, 3.00)	1.00 (–6.00, 4.00)	–0.425	0.671
AST changes (U/L)	0 (–2.99, 2.00)	–0.40 (–3.00, 2.00)	–0.051	0.959
Scr changes (mol/L)	0 (–4.00, 4.00)	1.27(–2.73, 5.00)	2.111	0.035
eGFR changes ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	0 (–4.40, 5.24)	–0.70 (–5.58, 4.23)	–1.168	0.243
WBC changes ($\times 10^9$/L)	0.03 (–0.50, 0.68)	0.15 (–0.52, 0.87)	1.167	0.243
NEU changes ($\times 10^9$/L)	0.03 (–0.48, 0.50)	0.08 (–0.46, 0.64)	0.813	0.416
HGB changes (g/L)	2.00 (–6.75, 2.00)	0 (–5.00, 4.00)	2.579	0.010
PLT changes ($\times 10^9$/L)	0.50 (–17.00, 17.75)	1.00 (–18.00, 15.00)	–0.312	0.755

Continuous variables were reported as median (25th percentile, 75th percentile). Categorical variables were presented as number (%). Comparisons between groups were performed using *t* test* or Mann–Whitney *U* test. The changes refer to the differences observed after 4 weeks of treatment compared with the baseline. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HGB: Hemoglobin; NEU: Neutrophils; PLT: Platelet; SBP: Systemic blood pressure; Scr: Serum creatinine; WBC: White blood cell; –: Not available.

Cluster 4 and 5. Details were shown in Suppelment Figure 5, http://links.lww.com/CM9/C303. Compared with the other two groups, patients in Group 1 had lower CV, SD and MAGE (all $P < 0.01$), lower TAR ($P < 0.05$), and higher sample entropies ($P < 0.05$). Patients in Group 2 had lower baseline HOMA-β and TIR (Group 2 *vs*. Group 1, Group 3: HOMA-β: 49.77 *vs*. 68.97, 69.65, $P < 0.05$; TIR: 79.73% *vs*. 85.39%, 83.26%, $P < 0.01$), higher $TBR_{3.0}$ and GRI (Group 2 *vs*. Group 1, Group 3: $TBR_{3.0}$: 2.41% *vs*. 0.55%, 0.40%, $P < 0.01$; GRI: 27.91 *vs*. 16.82, 18.74, $P < 0.01$), and patients in Group 2 had lower rates of reaching standard TIR, TBR, and responses ($P < 0.05$). Patients in Group 3 treated with acarbose had better responses in improving the CV, SD,

TBR, and GRI levels, as well as improving rates of reaching standard TBR and responses (all P <0.05) [Figure 3 and Supplementary Table 5, http://links.lww.com/CM9/C303].

The detailed process of time series analysis and major results including both the baseline and the endpoint variables are shown in Supplementary Materials [Supplementary Tables 5–9 and Supplementary Figures 4–7, http://links.lww.com/CM9/C303].

Discussion

To our knowledge, this multicenter, randomized, active-controlled study provides a new and strong evidence to date on the effects of acarbose and sitagliptin on TIR and GV in Chinese patients with type 2 diabetes. These data supported that acarbose had slight advantages over sitagliptin in improving GV and reducing the risk of hypoglycemia. At the same time, our study provided an innovative idea for utilizing CGM time series data and optimizing glucose management.

GV is a new indicator to measure the quality of glucose control. High GV is closely associated diabetic macrovascular and microvascular complications, hypoglycemia, and all-cause mortality.[14–17] For the evaluation of GV in AGI and DPP-4i treatment, previous studies provided some evidence but without head-to-head study.[4,18–21]

GV is strongly correlated with postprandial glucose excursions.[22,23] Multiple studies have confirmed that AGIs[18,24,25] and DPP-4is[23,26] can significantly reduce postprandial glucose exposure. Our analysis showed that acarbose was better than sitagliptin in controlling post-breakfast GV. The post-breakfast TIR levels were significantly higher in acarbose-treated patients than those in sitagliptin-treated patient, and the post-breakfast $TAR_{10.0}$ were significantly lower in acarbose-treated patients. This was consistent with previous study, which showed a highly significant positive correlation between increment in BG from the pre-breakfast value after an overnight fast to the 90-min post-breakfast value and SD around the 24-h mean glucose value.[27]

Further, rice and wheat are the main staple foods in China, and excessive intake of carbohydrates is an important characteristic of the dietary structure of Chinese residents.[28] AGIs are more suitable for patients with carbohydrate rich diets and postprandial hyperglycemia.[29] Besides, higher frequency of administration of acarbose (three times daily) than that of sitagliptin (once daily) may help patients pay much closer attention to their BG levels throughout the day, thus resulting in a better glucose control. Meanwhile, given the gastrointestinal symptoms associated with acarbose,[30] acarbose-treated patients showed decreased appetite, leading to reduced food intake and smaller postprandial glucose excursions than sitagliptin-treated patients. In addition, AGIs reduce postprandial glucose excursions independently of insulin secretion and its effects.[30] However, DPP-4is improve glucose regulation by increasing insulin secretion,[31] such hypoglycemic effect might be diminished by disease progression.

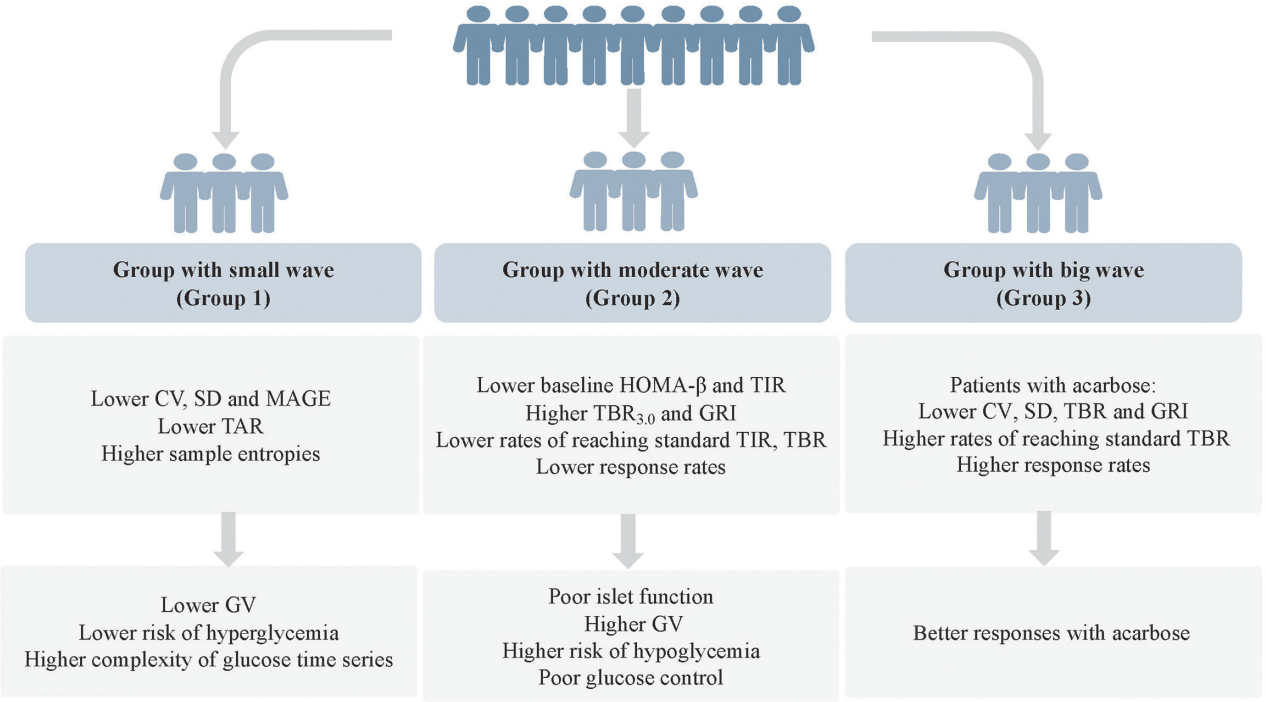

Figure 3: Major characteristics of clustering groups included in the trial of comparison of glucose fluctuation between metformin combined with acarbose or sitagliptin in Chinese patients with type 2 diabetes. Three groups were identified after time series decomposition, dimensionality reduction and clustering: group with small wave (Group 1), group with moderate wave (Group 2) and group with big wave (Group 3). CV: Coefficient of variation; GRI: Glycemia Risk Index; GV: Glycemic variability; HOMA-β: Homeostasis Model Assessment of beta-cell Function; MAGE: Mean amplitude of glycemic excursions; SD: Standard deviation; TBR: Time below range; TIR: Time in range.

AGIs do not stimulate insulin release when used as monotherapy and rarely cause hypoglycemia,[30] DPP-4is are generally not associated with an increased risk of hypoglycemia, either.[32,33] In our study, acarbose was more effective in reducing the risk of hypoglycemia than sitagliptin. However, one meta-analysis found no significant hypoglycemic differences among acarbose, DPP-4 inhibitors, and placebo after 48-week treatment.[34] Similarly, our results also showed that there was no significant difference in TBR level between the two groups at the later stage of CGM wearing.

GRI was a composite CGM metric of glycemic risk and provided a more accurate clinical picture by incorporating multiple dimensions of glycemic quality. There was high correlation between TIR and GRI.[12] Compared with conventional parameters, GRI reflected both the essential hypoglycemia and hyperglycemia components, gave more weight to extreme fluctuations, and correlated with clinician rankings more closely than other models such as HbA1c, TIR, or TIR combined with TBR. Furthermore, the hypoglycemia and hyperglycemia components can be plotted together on a grid, which makes it more visually to capture the glucose exposure.

Previous studies have shown that the complexity of glucose time series gradually decreased with the deterioration of glucose regulation.[9,34] Moreover, the complexity of glucose time series negatively correlated with FPG, postprandial glucose, SD and CV, and positively correlated with TIR and insulin secretion.[9] Consistent with these findings, higher complexity of glucose time series, as well as lower GV, was observed in Group 1. Our results suggested that CGI positively correlated with baseline body weight, BMI, FPG, fasting C-peptide, and TIR, and negatively correlated with CV, SD, MAGE, TAR, TBR, and GRI. Therefore, the complexity of glucose time series partly reflects glucose homeostasis system and GV.

In this study, there was no significant difference in the complexity of glucose time series between the acarbose and sitagliptin treatment. Hooijdonk *et al*[35] also indicated that the complexity of glucose time series mainly depended on endogenous factors, thus a much more longer treatment period was required for significant changes. However, as shown in Supplementary Figure 2, http://links.lww.com/CM9/C303, the entropy in the sitagliptin treatment was slightly higher than that in the acarbose treatment at scales of 1–6. This suggested that a greater improvement in glucose regulation might be seen in sitagliptin over a longer treatment period, which could be partly attributed to the advantage of sitagliptin in improving β-cell function.

RCMSE analysis provides a new perspective for CGM data mining. CGI is expected to become a new parameter reflecting impaired glucose metabolism and glucose fluctuations. There was a large prospective cohort study showed that the decrease of CGI was associated with an increased risk of all-cause mortality among type 2 diabetes mellitus (T2DM) patients with HbA1c <7%.[36] Further explorations are needed to see if CGI can be used as the endpoint in clinical studies on drug efficacy.

Time series analysis can reveal more important information about glucose fluctuation from CGM data. Previous study has proved that decomposition and clustering of CGM data generates representative CGM profiles that are predictive of 6-month therapeutic effects for T2DM.[11] Similarly, the present study used time series analysis as an effective tool to assess and predict GV and the risk of hypoglycemia, and to possibly identify populations with better responses to specific drugs. According to our results, we distinguished three groups of patients through time series analysis and clustering: one with lower TAR, GRI, CV, SD, and MAGE levels than the other two groups, one with lower baseline HOMA-β and TIR levels, higher TBR levels, and lower control and response rates, and one with superiority in improving the CV, SD, GRI levels and response rates in the acarbose treatment. According to our findings, patients in Group 2 should strengthen glucose monitoring, pay more attention to the risk of hypoglycemia and the glucose fluctuation. Meanwhile, acarbose should be the first choice for patients in Group 3 if meeting the indications, so as to optimize glucose control and reduce GV. It might provide guidance on individualized treatment for a better glucose control. This provided a new perspective to utilize glucose monitoring and optimize glycemic control. Further explorations are needed to expand the application of CGM in clinical data mining.

However, there are still some limitations in our study. First, choosing the appropriate intervention period and the optimal time of wearing CGM are vital issues that need to be further discussed. We experimentally use one month as the observation time to see whether AGIs and DPP-4i show differences in glucose fluctuations after one month. Randomized controlled trials with longer time are needed for further exploration. Though the two groups were generated by randomization to ensure the consistency in baseline glucose fluctuations, we believed that comparing separate CGM data before and after the intervention would provide more convincing information. Second, patients in the acarbose group had higher baseline body weights and lower AST levels than those in the sitagliptin group. However, these data in both groups were within the normal range and there were no differences in the changes of body weights and AST levels before and after treatment between the two groups. Third, only traditional measurements representing GV were evaluated in our study due to the complicated calculation of other metrics. Moreover, dietary structure and habits would have great influences in glucose fluctuations. Since most included patients were from Northern China, our results could not enough to represent patients in Southern China, where rice is the primary staple. In addition, we have not yet determined the specific relationship between the graphic characteristics and the clinical treatment outcomes. It is also unclear whether such methods can predict the responses beyond acarbose and sitagliptin. Different patients with different clinical conditions are needed to be verified by this method.

In conclusion, acarbose treatment had slight advantages in improving GV and reducing the risk of hypoglycemia when compared with sitagliptin treatment in Chinese

patients with background metformin treatment. Time series analysis of CGM data was helpful in predicting GV and the risk of hypoglycemia in patients with type 2 diabetes, and it was helpful in identifying populations with better response to specific drugs.

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Conflicts of interest

Linong Ji has received fees for lecture presentations and for consulting from AstraZeneca, Merck, Metabasis, MSD, Novartis, Eli Lilly, Roche, Sanofi-Aventis, and Takeda. No other support from any organization for the submitted work other than that described above. All other authors declare no competing interests.

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